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P R O C E E D I N G S

(1:00 p.m.)

DR. DRAKE: I would like to ask everybody to take their seat and please assemble.

Welcome to the Dermatologic and Ophthalmic Drugs Advisory Board meeting number 51. This is an open session regarding NDA 20-965, Levulan Kerastick for topical solution.

The first thing I will do is identify myself. I'm Lynn Drake. I'm professor and chair of the Department of Dermatology at the University of Oklahoma Health Sciences Center, and also hold a position of lecturer at Harvard Medical School, Massachusetts General Hospital.

I would like the panel to introduce themselves. I know you've done this before these last 2 days, but we have new players, so I would very much appreciate it if you would identify yourself by name and position, as well as what you do.

Dr. Stern, would you please start?

DR. STERN: Okay. I'm Robert Stern. I'm a professor of dermatology at the Harvard Medical School at the Beth Israel Deaconess Medical Center.

DR. MILLER: I'm Fred Miller. I'm director of dermatology at Geisinger Medical Center, Danville, Pennsylvania.

DR. DiGIOVANNA: John DiGiovanna. I'm director of the Division of Dermatopharmacology at Brown University, and an adjunct investigator at NIAMS of NIH.

MS. COHEN: I don't know what to say with all those things. I'm Susan Cohen. I'm a consumer member, and I also spend some time at the state attorney's office in Montgomery County.

DR. LIM: I'm Henry Lim, chairman of dermatology, Henry Ford Hospital, Detroit, Michigan.

DR. JORDON: Dr. Bob Jordon, professor and chairman, Department of Dermatology, University of Texas Medical School, Houston.

DR. MCGUIRE: I'm Joe McGuire, professor of dermatology and pediatrics at Stanford University.

MS. RILEY: I'm Tracy Riley. I'm the secretary of the Dermatologic and Ophthalmic Drugs Advisory Committee. I'm with FDA.

DR. KILPATRICK: Jim Kilpatrick, professor of biostatistics at the Medical College of Virginia.

DR. MINDEL: Joel Mindel, professor of ophthalmology and pharmacology at Mount Sinai Medical Center, New York.

DR. LAVIN: Philip Lavin, a biostatistician with Boston Biostatistics, and on the faculty of Harvard

Medical School.

MR. FELTEN: I'm not on the panel.

DR. DRAKE: That's all right. You're at the table.

MR. FELTEN: I'm Richard Felten. I'm the device reviewer for the NDA.

MS. FARR: Shahla Farr. I'm the biostatistical reviewer, FDA.

DR. OKUN: I'm Marty Okun, the medical reviewer for this NDA.

DR. WILKIN: Jon Wilkin, Dermatologic and Dental Division Director.

DR. DRAKE: Thank you.

I am going to announce a slight deviation in the order of business. Not in the order, but I want to announce the fact that we'll probably not take a formal break this afternoon in the interest of completing this deliberation in a timely manner. So for those of you that need a break, please feel free to just sort of slip out and take one.

And I would like now to ask -- oh, I'm sorry. Dr. Abel just joined us.

Would you mind identifying yourself and your affiliation?

DR. ABEL: Elizabeth Abel, dermatology,
clinical professor of dermatology at Stanford University.

DR. DRAKE: Thank you.

I'm now going to ask our executive secretary,
Tracy Riley, to give the conflict of interest statement.

MS. RILEY: Good afternoon. The following
announcement addresses the issue of conflict of interest
with regard to this meeting and is made a part of the
record to preclude even the appearance of such at this
meeting.

Based on the submitted agenda and information
provided by the participants, the agency has determined
that all reported interests in firms regulated by the
Center for Drug Evaluation and Research present no
potential for conflict of interest at this meeting.

In the event that the discussions involve any
other products or firms not already on the agenda for which
an FDA participant has a financial interest, the
participants are aware of the need to exclude themselves
from such involvement, and their exclusion will be noted
for the record.

With respect to all other participants, we ask
in the interest of fairness that they address any current
~~or previous financial involvement with any firm whose~~

products they may wish to comment upon.

Thank you.

DR. DRAKE: Thank you, Ms. Riley.

I'd like to ask Dr. Jonathan Wilkin to give his opening and introductory remarks about our business today.

DR. WILKIN: Thank you, Dr. Drake.

The questions for this afternoon are largely directed to labeling issues. The agency has already come to the conclusion regarding the approvability of this product. So I'll not read these in the interest of time at this time, but the committee has had these to review.

DR. DRAKE: Thank you, Dr. Wilkin.

The committee has the questions before them and the issues presented before them, so what I'd like to do now is go to the open public hearing. We've had no written requests for appearances today; however, the invitation is open for anybody to approach the open mike that wishes to.

If so, I would like you to identify yourself and any conflicts of interest or financial ties to the issue being discussed today.

(No response.)

DR. DRAKE: Seeing none, I think we'll move forward, then, with the rest of the program, and I would like to move now to the sponsor's presentation. It's DUSA

Pharmaceuticals, and are you Samuel Swetland?

MR. SWETLAND: Yes.

DR. DRAKE: Hi. Welcome. I would ask you to introduce yourself and all your fellow presenters, as well as your role.

And first thing, would you tell me what D-U-S-A stands for?

MR. SWETLAND: D-U-S-A is DUSA, and that's the name of the company.

DR. DRAKE: That is the whole name of the company?

MR. SWETLAND: DUSA Pharmaceuticals, Inc.

DR. DRAKE: Thank you.

MR. SWETLAND: Thank you.

I'm Sam Swetland of Guidelines, Inc. I am a regulatory consultant for DUSA Pharmaceuticals, and today we are here to discuss -- the first slide, please -- today we're here to discuss DUSA Pharmaceuticals' NDA for Levulan Kerastick for topical solution, 20 percent --

DR. DRAKE: Can you excuse me just one moment?

We need to have that off. There you go. Thank you.

MR. SWETLAND: NDA No. 20-965.

~~The Levulan Kerastick in conjunction with the~~

BLU-U blue light photodynamic therapy illuminator comprise a drug/device combination product. The primary mode of action for the combination product has been determined to be that of a drug, and the Center for Drug Evaluation and Research has been given administrative jurisdiction over the combination product. However, the Center for Devices and Radiological Health has review responsibilities for the premarket approval application for the device component.

This is a slide of an outline of the sponsor's presentation today. I will present some housekeeping issues and a brief introduction to the Levulan Kerastick NDA. Following my presentation, Dr. Stuart Marcus of DUSA Pharmaceuticals will present an overview of the Levulan photodynamic therapy. Next, Dr. Allyn Golub, also of Guidelines, Inc., will present the pharmacology and toxicology information that was submitted as part of the NDA. Then Dr. Marcus will return to present the Phase I and Phase II clinical study. Our last speaker today will be Dr. Daniel Piacquadio of Therapeutics, Inc., and the University of California at San Diego. He was one of the clinical investigators in our Phase III program, and Dr. Piacquadio will present the Phase III clinical data for the Levulan Kerastick.

~~This slide just gives a few definitions for~~

some terms that will be used throughout our presentation. Levulan is the registered trademark for DUSA Pharmaceuticals' brand of the active drug substance, aminolevulinic acid hydrochloride, or ALA HCl. The Kerastick is the trade name for DUSA's topical applicator dosage form. BLU-U is the trade name for DUSA's blue light photodynamic therapy illuminator. ALA will be used to refer to the endogenous form of aminolevulinic acid. And, finally, PDT stands for photodynamic therapy.

The Levulan Kerastick for topical solution, plus blue light irradiation using the BLU-U blue light photodynamic therapy illuminator, is indicated for the treatment of actinic keratoses of the face and scalp. The drug component of the combination product is the Levulan Kerastick. The Kerastick was specifically designed to segregate the active drug powder from the topical solution vehicle during distribution and storage, and to allow the rapid-add mixture of the two components just prior to its use.

Since this is a novel dosage form, we brought along a display containing the various components of the Kerastick, and we'll just pass a few of those around the room. In the meantime, this is a picture of the display.

~~The Kerastick is comprised of a dermatological~~

applicator tip and a flexible plastic applicator tube containing two sealed glass ampules. The glass ampules contain the appropriate amount of the active drug substance and the topical solution vehicle, when mixed together, to produce a 20 percent weight/volume topical solution. The glass tubes inside the applicator are shown over here on the right. This is placed within a protective cardboard sleeve, with a cardboard cap that covers the applicator tip during shipping and storage.

The drug application is conducted in the physician's office by the physician or health professional, and at the time of administration the two glass ampules are crushed through the applicator sleeve by pressing at the locations printed on the label, and the contents are mixed by shaking. Then the cardboard cap is removed, and the solution is applied to the target lesion by gently dabbing the lesion with the tip such that it wets the lesion, but does not drip or run.

The second component of the drug/device combination is the BLU-U blue light photodynamic therapy illuminator. Pictured here is one of the clinical units that was used in the Phase III clinical trials. The BLU-U is a compact non-laser light source that was specifically designed to provide uniform distribution of blue light to

the patient's face or scalp at a nominal wavelength of 417 nanometers and a power density of 10 milliwatts per centimeter squared. A premarket approval application has been submitted to CDRH and has been reviewed by that center.

Now I'd like to turn the presentation over to Dr. Marcus to describe how these drug and device components will be used in Levulan photodynamic therapy.

DR. MARCUS: Thank you, Mr. Swetland.

I'm going to introduce the section of this presentation dealing with the photodynamic therapy using Levulan and blue light. The first part will discuss the background mechanism and the pharmacokinetics, as well as dose administered and pharm/tox. The second part will discuss the Phase II clinical trials, which involved both drug dose ranging and blue light dose ranging. And, lastly, there will be discussion of the pivotal clinical trials utilizing the Levulan Kerastick and the blue light source.

ALA, aminolevulinic acid, is an endogenous molecule, and it's not a new molecule, but in the form of Levulan, it is a new chemical entity and a new drug. There is an extensive worldwide literature on photodynamic therapy using topical and systemic aminolevulinic acid

hydrochloride, and this molecule is rather unique in that there are two clinical conditions which may be looked upon as human models of chronic exposure to systemically overdose ALA and protoporphyrin, acute intermittent porphyria for chronic overdosing of systemic ALA and porphobilinogen, and erythropoietic protoporphyria as a model for chronic lifetime overdosing of protoporphyrin-9.

Photodynamic therapy is a type of photochemotherapy, which is a two-stage process, in that the photosensitizer is delivered and then activated by light. However, photodynamic therapy differs from other forms of photochemotherapy by its requirements for oxygen.

The therapeutic effects of photodynamic therapy are thought to be due to the production of singlet oxygen through the transfer of light energy through the photosensitizer to ground-state oxygen.

Using an endogenous photosensitizer such as ALA involves the following steps: Levulan is taken up by cells, converted first to ALA and then to protoporphyrin, which is a potent photosensitizer. As it accumulates, cells such as precancerous, malignant, or fast-growing cells can be identified by a characteristic fluorescence of protoporphyrin-9. And then if you expose those cells which accumulate protoporphyrin-9 to an intense light of

appropriate wavelength and energy, the PDT effect occurs, leading to cell death. In the case of Levulan PDT, the selective therapeutic benefit occurs due to selective drug application, followed by the accumulation of protoporphyrin-9 in the target cells.

This is the heme pathway, showing aminolevulinic acid as the first committed molecule in that pathway. The control point for the pathway is the regulation of ALA synthesis through ALA synthase regulation by the molecule heme, which is above the screen. When ALA is added exogenously, it bypasses the control point, and enzymes which are constitutively present, represented by the red line, are converted to protoporphyrin-9, which, through the addition of iron by ferrochelatase, becomes the non-photosensitizing molecule heme.

This is a simplification of protoporphyrin-9 accumulation, which we like to call the Levulan therapeutic pathway. It shows the Levulan Kerastick applying ALA hydrochloride to the skin surface, which then becomes ALA and enters the system after the control point. It's then rapidly converted to protoporphyrin-9. Protoporphyrin-9 builds up rapidly, exceeding the capacity of ferrochelatase to remove it, and, therefore, accumulates within the system when light is then shone on the system, such as the BLU-U.

The therapeutic benefit occurs through the production of singlet oxygen.

But one must remember that ferrochelatase provides an escape mechanism by which excess protoporphyrin-9 is rapidly converted, then, to heme, which is a non-photosensitizer. Also, the very active shining of light on protoporphyrin-9 for PDT produces a photobleaching effect, removing excess drug.

I'd like now to introduce Dr. Allyn Golub, who will speak.

DR. GOLUB: Thank you, Dr. Marcus.

My presentation today will be divided into two sections. First, I'd like to discuss the pharmacokinetics/bioavailability and how we estimate the dose of Levulan that's administered topically. Secondly, I'll briefly discuss the preclinical toxicology studies that were conducted with this compound.

As Dr. Marcus indicated, aminolevulinic acid is a well-described endogenous compound that's found in virtually all living organisms as a precursor in the porphyrin biosynthetic pathway leading to the formation of heme and chlorophyll.

For pharmaceutical purposes, we use the hydrochloride salt of aminolevulinic acid, just known as

Levulan. This is an odorless, white to off-white crystalline powder with a molecular weight of 167.59. It's freely soluble in water, slightly soluble in alcohol, and practically insoluble in most organic solvents. The drug completely dissociates in aqueous solution, leading to a solution with low pH. The primary degradation product in solution is pyrazine 2,5-dipropionic acid that's formed by the autocondensation of two aminolevulinic acid molecules.

The vehicle for Levulan administration is comprised of common dermatological excipients and has about 50 percent alcohol.

Studies were done in both humans and dogs to characterize the systemic bioavailability and pharmacokinetics of Levulan to basically confirm what's already well described in the literature. In this particular slide, we're showing the results from a study in six normal male volunteers who were administered 128 milligrams of Levulan intravenously and orally, and the time concentration curve generated over a period of 8 hours. The important information on this slide is that the drug is very rapidly cleared from the systemic circulation that occurs following both intravenous and oral absorption, and that the oral bioavailability is lower than the area under the curve for the intravenous dose; in fact, it's

about 60 percent bioavailable in this particular study.

This table summarizes the results from that human study as well as a dog study. The IV half-life here was about 50 minutes, very rapidly excreted. In the dog it was about 20 minutes. The PO half-life was about 40 minutes in both species. And the relative bioavailability, as I said, was 60 percent in the humans in that study, and about 40 percent in the dogs.

I should mention that we also monitored protoporphyrin levels in this study. The levels were very, very low, they were erratic, and beyond 12 hours they were undetectable at the limits of the sensitivity of the assays that we used.

Based on the wealth of data that we've generated in our developmental process, we're able to estimate the amount of Levulan that would be administered topically using the Kerastick as directed in the package insert and its potential systemic availability. From in vitro studies, several that were done during product development, we've calculated that approximately 2 milligrams per centimeter squared of Levulan will be applied in two successive applications as directed in the package insert.

~~In our Phase II studies, ALA-007 and -017, we~~

carefully measured the AK lesion surface area that was randomly chosen for application of the drug. This turned out to be approximately half a square centimeter per lesion. In our Phase III studies, ALA-018 and -019, physicians were allowed to apply the drug to four to 15 lesions per patient. Seventy-five percent of the applications were less than 10 lesions, but we're going to err on the high side and assume, let's say, 15 lesions are applied per patient. As a matter of fact, all of these values were chosen to be on the high side of the numbers that we calculated.

So simply by multiplying the quantity of Levulan applied times the lesion surface area that it's being applied to, times the total number of AK lesions treated, we can calculate that approximately 15 milligrams of Levulan would be applied per patient, and that's equivalent to about 12 milligrams of ALA. You divide that for a 70-kilogram individual, and it indicates that less than .2 milligrams per kilogram of aminolevulinic acid would be applied to the patient.

Now, we've done in vitro studies through cadaver skin, again, using exactly the methodology described in the package insert for application in the Levulan topical vehicle, both to intact and stripped

cadaver skin, in which the stratum corneum was removed. In intact skin, we see about -- and this, again, is on the high side -- approximately 2 percent of the drug passes through the skin into the receptor fluid over a 16-hour dosing interval. In stripped skin, in which the stratum corneum is totally removed, we see upwards of 30 percent over 16 hours. However, even if we assume 100 percent of that 12 milligrams of ALA is absorbed systemically, we calculate that that would be only about 3.5 percent of this number, 350 milligrams per day, which is believed to be synthesized by the human body to support endogenous heme synthesis.

With these numbers in mind now, let's turn to the preclinical toxicology program that was conducted for the drug.

Acute toxicity studies were initially done in mouse, rat, and dog. In mice and rats, doses up to 300 milligrams per kilogram were administered intravenously with no adverse effects. This was a standard battery of measurements that was used to characterize the -- these studies were GLP studies. In the dog, 100 milligrams per kilogram led to some excessive salivation and vomiting and transiently increased aspartate and alanine aminotransferase activities, particularly at the 100-

milligram-per-kilogram dose. These increases were judged to be mild to moderate and were very transient, lasted for a very short period of time.

In the skin studies that were conducted with this product, we did subcutaneous administration of the drug up to 1,000 milligrams, a gram per kilogram, and found dose-dependent irritation and/or the formation of lesions at the site of injection. There were no other systemic findings made, and these effects were judged to be a result of the high ionic strength and low pH of the solutions that were administered.

In rabbits, we have evaluated topically the effects of the topical solution and the topical cream. The results in both of these studies, up to 30 percent ALA showed slight to moderate dermal irritation with both the vehicle and the formulation.

I'd like to focus a little bit further on this study, the topical solution, because this is the product that's under consideration here.

There were 20 male and 20 female rabbits in the study. The body weight was approximately 2 kilograms. The drug application area was over 180 square centimeters on the back of the animal. The skin was prepared by clipping it free of hair, and then the epidermis was abraded to

allow penetration of the drug through the stratum corneum.

As I indicated, doses up to 30 percent of the topical solution were applied. It was applied at a dose of 2 grams of the solution per kilogram of animal body weight under occlusion. There was no light exposure in the study, but the skin was completely occluded for a period of 24 hours.

This table summarizes the results found in this study. You see even with vehicle there was slight to moderate erythema. That tended to increase to moderate at the highest concentration. There was some edema, desquamation, and coriaceousness and fissuring actually occurred primarily at the highest dose. In general there was only slight to moderate irritation detected in the study under pretty stringent conditions, under occlusion for 24 hours.

Finally, a battery of mutagenicity protocols has been conducted with the Levulan product. This includes the salmonella, E. coli, and mammalian microsome reverse mutation assay, which is also known as the Ames test, at doses up to 5,000 micrograms per plate, plus or minus metabolic activation. The end result of this study was that there was no increase in revertants.

I should mention this says, "with a confirmatory assay." All of these assays were done twice

in succession, a complete replicate of the study, just to confirm the results obtained the first time.

Similarly, an Ames test with solar light radiation to look for photoproducts of ALA during incubation was conducted up to 5,000 micrograms per plate.

Again, no increase in revertants, with or without solar light radiation. Mouse lymphoma also was negative, plus or minus metabolic activation. There's no evidence in these studies that there is mutagenicity. And, finally, in the in vivo mouse micronucleus assay, not only was there no increase in micronuclei, indicating low or no potential for genotoxicity, but also the dose of 1,600 milligrams per kilogram was well tolerated by the animals in the study. So overall it showed a very comfortable side effect spectrum.

Now I'll turn the program back to Dr. Marcus, who will describe the Phase I and II studies that were done with this compound.

DR. MARCUS: Thank you, Dr. Drake, and thank you, Dr. Golub.

I'll be starting off the clinical data summary with the controlled clinical trials that were used to support and define the Phase III pivotal study.

~~The first was a Phase II light dose ranging~~

study using blue light and 20 percent topical Levulan solution. ALA-007's study design was of a randomized, vehicle-controlled, and investigator-blinded multicenter study in which the Levulan solution was applied to individual AK lesions on 36 patients. There were three clinical trial sites, and because two lesions were treated with either Levulan or vehicle, the complete patient response was judged to be as patients with 100 percent of AK lesions cleared.

At Week 8, which is the primary efficacy time point, there is a trend, as you can see. The blue light doses were 2, 5, and 10 joules per square centimeter, delivered at either 3, 5, or 10 milliwatts per square centimeter power density. If you look at the 10-milliwatts-per-square-centimeter bar, you see a trend toward a dose/response with a maximal dose/response of 80 percent after a single treatment with light and drug.

The summary of this study showed, again, up to 80 percent of patients completely responded to a single treatment with topical Levulan and blue light, and 10 joules per square centimeter delivered at the highest power density provided the best results in that study.

In the safety profile, mild to moderate stinging and burning was observed, mostly during light

treatment, and this will prove to be a constant throughout the studies you'll be seeing this afternoon. There were no treatment-related significant adverse events and no systemic photosensitivity observed.

Another blue light dose ranging study was done as a safety study, ALA-016. Again, this was a randomized, vehicle-controlled, investigator-blinded multicenter study, with 64 patients randomized. Here the 20 percent Levulan solution was applied to a 25-square-centimeter area of skin containing three to seven AKs, photodamaged skin. There were three clinical sites, as before, and here, because of the larger number of AKs treated, we were able to define the complete patient response as patients having greater than or equal to 75 percent of their lesions completely cleared.

The results of this study show that, again, if you look at the 10-milliwatts-per-square-centimeter bar, we saw 100 percent responses in all three doses of light, but the most consistent result was 100 percent response at 10 joules per square centimeter.

In this study, up to 100 percent of the patients, by our definition, completely responded to a single treatment with topical 20 percent Levulan and blue light. Again, 10 joules per square centimeter gave the

best result, and this, of course, was consistent with the first blue light dose ranging study.

In the safety results -- and this was done as a safety study -- there was stinging and burning during light treatment, and there were no treatment-related significant adverse events or systemic photosensitivity. However, the discomfort of stinging and burning was increased as a result of applying Levulan 20 percent solution to a larger area than single AKs, individual AKs, and in this study 6 percent of the patients had PDT treatment terminated early, and 9 percent reduced the power density due to the discomfort of stinging and burning as a result of the larger-area application. We took that as support of the labeling statement to apply Levulan solution to individual AKs.

A Phase II drug dose ranging study was carried out using blue light at 10 joules per square centimeter, delivered at 10 milliwatts per centimeter. In this study, we evaluated the safety and efficacy of Levulan topical solution at 2.5, 5, 10, 20, and 30 percent weight-to-volume solution. Again, this was randomized, vehicle-controlled, and investigator-blinded, and multicenter, but this one was the first study statistically sized to detect the difference between Levulan 5 percent and Levulan 20 percent

solutions. One hundred and twenty-four patients were accrued to this study from eight clinical trial sites.

Next.

Here are the efficacy results, graphed by both lesion response rate and patient response rate, using patients who have greater than or equal to 75 percent of their lesions completely clearing judged as patient complete responders. As you can see, there is a dose/response evident in the study, with a plateau emerging at 10, 20, and 30 percent. For the patient responders, the best dose was 20 percent in this study.

All three 10, 20, and 30 percent Levulan solution concentrations were significantly better than the 5 percent solution, and that's shown here.

In the safety study, because of a larger number of patients, we were better able to characterize the stinging and burning, and, again, there was primarily stinging and burning during the light treatment, but it was very subjective. There was no clear drug dose/response. It was also transient and resolved rather rapidly on the termination of light treatment. There were no treatment-related significant adverse events and no systemic photosensitivity again, and the fact that there was no clear drug dose/response to the burning and stinging is

shown by the fact that two patients out of 124 had their PDT treatment terminated early for discomfort, or burning and stinging, but one had 2.5 percent Levulan applied and one had 20 percent.

We were also able to objectively characterize what is termed the PDT response to Levulan PDT, and it consists of lesional erythema and edema, which peak 24 hours after the light treatment, it's transient, and rarely, if ever, requires medication.

The conclusion from these Phase II studies was that we would use Levulan 20 percent topical solution and blue light at a dose of 10 joules per square centimeter, delivered at 10 milliwatts per square centimeter, for the Phase III pivotal trial.

I'd like now to call Dr. Dan Piacquadio to discuss the Phase III clinical trial design, safety, and efficacy results.

DR. DRAKE: Dr. Lim, you have a question for clarification?

DR. LIM: Clarification, yes.

On the 016 and 017 study, you have, I think, six patients and two patients stopping treatment before treatment was completed because of the stinging sensation.

~~Were those patients included in your data analysis, or~~

were they dropped from data analysis?

DR. MARCUS: They were dropped from that data analysis of that study. But I think we'll have a fuller report of all patients in the Phase III study.

DR. PIACQUADIO: Thank you.

I'll apologize in advance for any coughing or hacking. I have a bit of a cold with postnasal drip, but I think we'll be all right.

I have the pleasure today to present the data for this trial. It's unusual to have the chance to talk about a new class of therapy in dermatology, and I appreciate the opportunity for DUSA Pharmaceuticals inviting me to speak here today.

Basically this pivotal trial was divided into two Phase III studies of photodynamic therapy with Levulan topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp. The objective of these two pivotal studies was to prove the safety and efficacy of Levulan 20 percent solution and the 10-joules-per-centimeter-squared blue light delivered at 10 milliwatts per centimeter squared in the treatment of multiple actinic keratoses, again, of the face and scalp.

I'll now talk about a few of the key elements of the design. These Phase III studies were vehicle-

controlled, investigator-blinded, multicenter, randomized, uneven parallel group studies in patients with multiple AKs of the face and scalp. The aggregate enrollment was 243 patients for both trials, and, again, all qualifying with four to 15 target lesions on the face or scalp area.

This is an outline of the procedures throughout the trial. There are a few key points of note. The duration of the trial was 12 weeks. There were two treatment opportunities, one at baseline and another at Week 8. The Week 8 treatment point was for those lesions, be it active or vehicle-treated, that did not fully respond. And then during the course of the study, adverse events in PDT response were documented at every visit.

With respect to both of these trials, a very experienced group of clinicians well known for their activity in the clinical research arena was incorporated into both trials, and they represented a diverse geographic distribution as well.

Now we're going to review some of the highlights of the key inclusion and exclusion criteria that were applied. In this trial, male or non-pregnant female outpatients over the age of 18 years were enrolled. Females were either postmenopausal, surgically sterile, or ~~were using an acceptable form of medical contraception and~~

had a negative urine pregnancy test to enter the trial. And, again, they all met the same criteria of having four to 15 target lesions on the face or scalp.

With respect to key exclusion criteria, patients with a history of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins, or photodermatitis were excluded. Any use of photosensitizing drugs and very thick or markedly hyperkeratotic actinic keratoses were excluded. Now, the AKs were graded on a scale of 1, 2, and 3. Moderately hyperkeratotic lesions were treated, and we'll see some photos of those cases.

Primary exclusion criteria regarding use of other therapeutic modalities before entry in the trial are highlighted here. Within a 2-week period, topical medications such as steroids, alpha-hydroxy acids, or retinoids were excluded. Within 4 weeks, systemic steroid therapy was precluded, and within the 2-month category, cryotherapy, laser therapy, chemical peel, topical 5-FU or Actinex treatment, systemic treatment with chemotherapeutic agents or any other immunomodulating drug or systemic retinoids were excluded.

Now we're going to talk a little bit about the activities at some of the key visits throughout the trial.

~~One of the things to note in this trial design is, since~~

PDT is an obvious therapeutic event, you can usually see it, this study design incorporated the use of both unblinded as well as blinded investigators. For this initial Baseline Visit A, which occurred 14 to 18 hours prior to light treatment and within 2 weeks of the original screening visit, again, the four to 15 target lesions were identified. They were numbered, documented, and graded by the evaluator, and photographs were also taken. Then, at that point in time, any PDT-like characteristics were evaluated.

The next activity at that visit was for the unblinded investigator only. Key activities included drug or vehicle application as per the protocol, which we'll talk about in a moment. Concomitant medications or adverse events were noted. And, most importantly, the patients were told to avoid light exposure and not to wash the areas where the drug was applied.

This is a demonstration of the application, and as Sam had talked about before, it's a pretty simple tool to use. There are two marking points on this cylinder that show you where to break the two ampules within it. Then you shake for a period of 2 to 3 minutes to mix the drug adequately, and then you basically simply dab on each actinic lesion individually, and in this trial that

procedure was performed twice for each of the individual lesions. It was very simple, easy to control, well tolerated by the patients.

Now we're moving on to the Baseline Visit B activities. Again, you should note that this is an unblinded investigator activity. This is referring to the pretreatment assessment, which is basically 14 to 18 hours after application of Levulan. At that time clinical signs of cutaneous reactivity with respect to erythema, edema, stinging and burning were evaluated on the 0 to 3 scale, shown here. Similarly, at that same visit, again, by the unblinded investigator, patients' subjective evaluation of stinging and burning intensity associated with the target lesions was graded on a similar scale, 0 to 3, none, mild, moderate, severe.

Now with respect to the light treatment aspect of this visit, again, performed by the unblinded investigator, the target lesions were rinsed off, then patted dry, and then they all received the uniform light treatment as specified in the protocol, the 10 joules per centimeter squared at a power density of 10 milliwatts per centimeter squared, for approximately 1,000 seconds, or 16 minutes and 40 seconds, of treatment light time.

~~This is an example of a patient receiving light~~

therapy. You can see a nice, uniform application of light over the treatment zone, which is the face in this case. In general the light is actually very easy to use and convenient for the patient as well.

Moving on to Baseline Visit B for the unblinded investigator with respect to actually characterizing the PDT response, there were two key areas of note, objective and subjective criteria, looking at the clinical manifestations of the PDT response reviewed earlier as well as by Dr. Marcus, and then the subjective assessment of stinging and burning. With respect to the stinging and burning, that assessment was done temporally during the entire treatment at 1, 6, and 11 minutes. Later when we start talking about the actual data results, if a patient had a severe notation at one of the time frames, they were frequently amalgamated or talked about having a severe burning or stinging response.

But what's important to note is that this is a temporal event, and actually when you treated these patients, in general the reaction from a stinging and burning perspective was really mild to moderate. It was very unusual to have a patient react such that they wanted to discontinue the treatment. In fact, there were only six subjects throughout the trial.

Another problem here is the variability of the definition of what severe, moderate, mild means. There were no definitions given, and this is not a "professional" evaluator, it's a patient, and we all know the variability of what that definition or word means to each person.

Additionally, and lastly, at this visit other PDT-like reactions -- crusting, scaling, et cetera -- were also evaluated.

Follow-up visits were at 24 hours, as well as at Week 1, 4, 8, and 12, respectively. Efficacy evaluation, again, was the domain of the blinded investigator, performed at Week 4, 8, and 12, and, again, to assure the blinding, separate case report forms were used here so that that evaluator had no knowledge of the unblinded investigator's activity in the trial. Assessments of the PDT response were also done, as well as adverse events and concomitant medications.

Now we're going to talk about the efficacy parameters for this study. The primary efficacy parameters are highlighted in this slide. Basically we're looking at lesion counts performed at baseline, as well as follow-up visits at Week 4, 8, and 12, respectively. And for the purposes of this trial, the protocol defined Week 8 as the primary temporal efficacy endpoint. Analyses included the

percent of lesions that completely responded, the percent of patients that had a 75 percent or greater reduction in their lesion count, and the percentage of patients with 100 percent reduction in their lesion count.

I'll take a moment here to sort of clarify this nomenclature. It's a little confusing the way the term "complete response" is used in the protocol. In general when people think of complete response, they think of cleared. In this first category, that's what complete response really refers to, basically clearing of the lesion. The other two criteria refer to, of the lesions in that patient, four to 15, did 75 percent or greater or 100 percent of them totally clear? And we'll review that when we go to the charts for the efficacy results.

Secondary efficacy parameters included the cosmetic response of each lesion, again, evaluated at Week 4, 8, and 12. The overall cosmetic response of each lesion was, again, graded on a four-point scale, from excellent to poor, as shown. And the patient evaluation of cosmetic response was also performed, but only at the Week 12 time point.

Now, for those patients that did not have all their lesions completely respond, be they drug-treated or ~~vehicle-treated, they were retreated at Week 8 using the~~

same methodology as the baseline visit that we reviewed earlier. These patients also had repeat follow-ups at 24 hours, as well as one week later, at Week 9.

Now, the importance of this slide is it shows the disposition of patients in both pivotal trials. Of note, I think, there were 243 patients enrolled, of which only 10 in aggregate discontinued from the trial. Whenever you have a trial that really only has a therapeutic intervention of benefit sort of at the beginning of the trial and nothing for 12 additional weeks, to have a dropout rate in the range of 4 to 5 percent is pretty unusual.

The other thing to note here in this trial is that the distribution of dropouts for both the vehicle and Levulan treatment categories were essentially equivalent, and, similarly, there was no real trend with respect to the reasons for discontinuation in either of the groups, be they vehicle or active.

Now, this is a bar chart that summarizes the efficacy results per the protocol. What we have here on the X axis is the 018 data and the 019, and then the pooled data of both studies together. This goes to the issue of a little bit of confusion, at least for me, with respect to nomenclature, using this term "complete response" that has

a variety of definitions. I think it's easier to view this as the response percentage based upon two criteria that are outlined to the right. The turquoise-colored bar refers to those patients where 75 percent or more of all the lesions treated in that individual, be it four to 15, cleared. The brown color refers to those groups of patients where 100 percent or all of the lesions treated in those patients completely resolved. And similarly for the vehicle-controlled groups that are pink and yellow, respectively.

Key points of note on this chart, from my viewpoint, are as follows. There is basically good agreement between the two pivotal trials for both the active treatment groups and the vehicle treatment groups. There is obviously a marked statistical difference between active and vehicle for both studies. Essentially there is approximately a 77 percent response rate when one applies the greater-than-or-equal-to 75 percent criterion. With the more stringent 100 percent criterion, the rate decreases to approximately 66 percent. And the vehicle response rate, irrespective of what criterion is applied, is somewhere in the range of 10 to 18 percent.

Now, I know there was a question posed by the agency regarding the use of these different criteria, 100 percent and 75 percent. As a developer in the realm of

dermatology, it's very rare for us to have great therapeutics where the reasonable clinical endpoint as a doctor is complete resolution. The reality is, most tools we use in dermatology are modest in their therapeutic intervention. However, when you're trying to fully characterize the performance profile of a drug, it is very helpful to know what is the complete resolution as an endpoint. As a clinician, though, most drugs that we use, the expectation clinically is a very good clinical response, which would probably be, again, in that area of 75 percent or so.

So to me both of these variables are very important. One, if I'm trying to really get a handle on the performance index of the drug and want to know what it does as a perfect therapeutic intervention, the 100 percent criterion is extremely helpful. As a clinician practicing my craft, the idea of what does that 75 percent level mean is probably more important to me, because that gives me an idea of what's reasonable clinical expectation for using that therapeutic modality and understanding and making a best-choice decision for my patient.

Now, this is the data for Week 8, and now we're going to move on to the longer time point, which is the ~~Week 12 evaluation. Again, the presentation of the data is~~

the same. On the X axis, the 018 data and the 019 data separate, and then pooled together. The Y axis, again, viewing it as response percent, and the two different criterion are 75 and 100 percent, respectively. Very similar in that we see relatively consistent agreement between the two trial groups in the marked difference between active and any vehicle effect, and in the pooled data response, with respect to the criterion of 75 percent or more, roughly about an 89 percent response. Applying the 100 percent criterion, we see approximately a 72 percent response.

Now we're going to look at a few clinical photos. This is an actinic keratosis in the preauricular area. This would be typical of a Grade 2 lesion. It is moderately hyperkeratotic.

The next slide we're going to look at shows the response 24 hours after therapy, and this is a pretty classic PDT-like reaction, with diffuse erythema surrounding the lesion area, maybe scant edema, and in this particular case, a small amount of superficial erosion. Now, these characteristics resolve pretty quickly. Healing is usually over several days, with complete resolution of any type of sign or symptom usually within about a week.

~~This is the same patient at a Week 12 time~~

point, and we can see the area is resolved, with no residual actinic keratosis remaining.

This is another patient that has a well-marginated, but rough hyperkeratotic lesion that has a nice juxtaposition to her hairline, to identify its location. Here, again, at 24 hours we see a similar PDT reaction, with scant erythema, probably a little less erosion, and maybe some trace edema. And then this is the Week 8 time point, which was the primary evaluation time point. There is no residual remaining.

~~This is the final case. The lesion is right~~ here. It sits between the hairline and these two landmarks, to help orient everyone. Here we see a similar response, no erosion, but you can see there's a little more diffuse area involved with erythema, and potentially a little edema. And then, again, here is the 12-week time point, resolution of the lesion.

A summary of the secondary efficacy parameters with respect to cosmesis, we can look at the investigator-rated cosmetic response being graded as excellent or good.

I believe these data are reversed. The 018 is actually 94 percent, the 019 is 90 percent, with an average of basically 92 percent, equivalent between the two trials.

~~With respect to patient evaluation at the Week 12 time~~

frame, again, 93 to 94 percent, respectively, for the 018 and 019 trials, a high degree of correlation between the two evaluators, experts and subjects.

With respect to safety summary for the two trials, the burning and stinging was reported during PDT, and it peaked during the first minute. Light treatment was discontinued in two of 88, or 2 percent, of the Levulan-treated patients in 018, and four of 93, or 4 percent, of the Levulan-treated patients in 019. No significant treatment-related adverse events were appreciated, and, similarly, no systemic photosensitivity was appreciated.

With respect to the PDT response with regard to erythema, it was present in a great majority of patients at baseline. After light treatment, 99 to 100 percent of the patients had erythema, but it quickly resolved to near-baseline levels by Week 1, and the majority of it resolved over a few-day period.

With respect to edema, it was present in a far less number of patients, less than 1 percent, at baseline.

After light treatment, it was seen in 28 to 41 percent of patients, and the edema also resolved to near-baseline levels after one week post-light treatment.

This slide characterizes the evaluation for pigmentation. It basically looks at pigmentary changes

compared to baseline, which is not shown, at the Week 8 and Week 12 time point. Of real note here is that in general the preponderance of lesions, both in the active Levulan group as well as the vehicle group, have really no significant change in pigmentation. So from a therapeutic side effect standpoint, this therapeutic intervention has no net effect on pigmentation.

So in summary, looking at this first bullet, this applies to applications of that criterion that refers to 75 percent or greater response rate. Seventy-seven percent of patients completely responded to Levulan PDT by Week 8 post-treatment, increasing to 89 percent by Week 12.

If we apply the more stringent criterion of 100 percent, these numbers change to about 66 and 72 percent, respectively, for Week 8 and Week 12.

Consistent PDT responses were burning and stinging during light treatment and transient post-PDT lesional erythema and edema, which, again, resolved at the baseline levels within one week.

The cosmetic response is deemed to be good or excellent by the investigators in 92 percent of the lesions, and that number is in agreement with what the patients predicted or assessed as well. And, again, no pigmentary changes were seen as a result of therapy.

I thank you for your attention.

DR. MARCUS: This concludes the sponsor's presentation.

DR. DRAKE: I'd like to thank all the sponsor's presenters, and I thank you for being cognizant of the time. That was a very thorough presentation, and right on the button time-wise, and it was clear. So we appreciate it.

I would like to ask for some questions now. I'd still like to keep this on the clarification part until we get to the actual discussion phase, but I would like to call for clarification questions.

Dr. Lim?

DR. LIM: Yes, a clarification question for Dan.

Dan, on the clinical slides, there are two slides, I believe, where there is erythema following treatment on an area that appeared to be beyond the lesion site. Do you know if that is the effect of the ALA on normal skin, on clinically normal skin, or is it the effect of ALA on probably a subclinical lesion?

DR. PIACQUADIO: We're waiting to get the mike turned up, I guess.

DR. DRAKE: It's on.

DR. PIACQUADIO: If you look at that dab-o-matic tip, which I'm happy to pass around, it does have a surface area that's bigger than many AKs, so by using that tip, you're absolutely getting drug applied to the lesion as well as perilesional skin.

As you know as well as I do, AKs are a manifestation that is clinically seen at one point, but is a continuum, and the adjacent skin especially in patients enrolled at my site is probably markedly photodamaged, whether you can clinically assess an AK or not.

So to your question in specific, I think what you're seeing is a combination of things. You may be seeing a true therapeutic selective effect in some patients that is related to an AK treatment that's subclinical. In some other patients, you have an inflammatory cascade that is not totally respecting the area of drug application and extends somewhat out beyond that.

DR. LIM: Thank you.

DR. DRAKE: Dr. Stern?

DR. STERN: To follow up on that question, do you have Phase I data in normals looking at the erythema effect of this application of agent in non-sun-exposed normal volunteers with these doses of light? I think that will tell us at least whether we have to be concerned about

this being applied, even inadvertently, to areas that aren't sun damaged.

DR. MARCUS: We have not specifically done studies on areas that are non-photodamaged.

DR. STERN: There was never any dosimetry done in terms of normal skin and erythema with this topical agent?

DR. MARCUS: We have treated a variety of conditions, which include basal cell carcinoma, psoriasis, and actinic keratoses, and in all cases the Levulan was applied to the lesional skin. The only time it was applied to perilesional skin was in the ALA-016 study, which we do have slides of, but that is photodamaged skin.

There are anecdotal reports, and our investigators have done studies which are not done as a sponsor phase GCP study, and I can tell you that if you apply Levulan to normal skin, let's say on the arm, a non-sun-exposed area of skin -- and, again, this is anecdotal, I don't have a clinical trial to show you -- the length of time it takes to become photosensitized far exceeds that of the lesion, including actinic keratosis lesions.

DR. DRAKE: Do you have a follow-up comment?

There's a mike back there that's a standing
~~mike or this hand-held mike. If I could ask everybody to~~

please be at the mike to speak.

DR. PIACQUADIO: I think the fundamental issue to that question is really one of safety, and I think the one compelling fact with the treatment here is, although we didn't do any comparative studies with 5-FU or cryo, with respect to healing course in these patients, they healed much more readily than 5-FU for sure, cryo maybe -- it's a little hard to tell -- but absolutely banally. I mean, these people don't have pigmentary or textural changes, at least within the 1,400 or so lesions that were treated in this study.

DR. STERN: I was going to leave this question for later, but since you brought up this issue, I think one issue to me is, if you ask me how much cryo does it take to get rid of an actinic keratosis so it will look good in 8 or 12 weeks, that's very different than how much cryo does it take to have a high probability of this lesion not returning within a year or two, and I'm wondering, do you have any plans specifically or has this cohort been followed with respect to recurrences over what I would consider a clinically relevant period of time? Making AKs better for 3 months is not a clinically relevant period of time.

~~DR. MARCUS: There are published reports using~~

other studies that AKs after a single treatment do not recur for a period of at least a year. What we have agreed to with the agency is to conduct a postmarketing study in patients, following them for 1 year to look for recurrence.

DR. DRAKE: I want to be careful we don't get too much off into discussion here, because I think the FDA will address -- remember, the FDA has deemed this efficacious, so efficacy is not an issue before us today.

Jon?

DR. WILKIN: I just wanted to mention a possible asymmetry. Dr. Marcus mentioned some anecdotal sorts of studies on normal skin, and I don't recall that being submitted with the NDA.

DR. MARCUS: No, they were truly anecdotal, and I did not use the word "published."

DR. WILKIN: But basically what we do is, at the FDA, strictly speaking, we don't review drugs, we review information about drugs, and we review the information that has been submitted by the sponsor. So if you're going to bring information up here that we haven't had a chance to review, I think it's important that you identify whether we've had a chance to review it or not.

DR. MARCUS: Point well taken. Thank you, Dr.

Wilkin.

DR. DRAKE: Dr. Jordon, and then Joe.

DR. JORDON: Just one clarification so that I'm sure I understand. What's the time sequence between application and the phototherapy?

DR. PIACQUADIO: Per the protocol, it was defined as 14 to 18 hours.

DR. JORDON: Fourteen to 18 hours. Thank you.

DR. DRAKE: Dr. McGuire?

DR. MCGUIRE: I had a little trouble with the data, but that's my problem, I think, not the presenter's. How do you score lesions that disappear 75 percent or appear to be nearly gone?

DR. PIACQUADIO: Well, again, I probably didn't make that clear. That criterion refers to the fact that 75 percent or more of the lesions completely cleared. So if the individual had four lesions, for them to meet that criteria, three or more of their lesions were completely resolved.

DR. MCGUIRE: I'm glad you clarified that.

DR. PIACQUADIO: Sorry if that wasn't clear.

DR. MCGUIRE: That makes it look a little different. Did you then further explore these lesions to see if there were histologic differences between the responders and the non-responders?

DR. PIACQUADIO: Again, in this pivotal trial design, biopsy evaluation was not performed. The only thing that was done is, those lesions, be they treated with vehicle or active, at the 8-week time point were retreated if they still persisted on a lesion-by-lesion basis.

DR. MCGUIRE: You did very extensive and very careful dosage studies on concentrations of ALA. Did you similarly perform time duration studies, or did you pick 1,000 as a good number?

DR. PIACQUADIO: Well, again, I'll probably defer to Dr. Marcus.

Do you want to answer the dose ranging question?

DR. MARCUS: I didn't hear the full question. You said 1,000, being 1,000 seconds of --

DR. MCGUIRE: The question was, you did very careful dosage studies with ALA, but then told us that you exposed the patients for 1,000 seconds, and I wondered if 1,000 was arrived at after some clinical experience.

DR. MARCUS: Oh, yes, that was a result of the two light dose ranging studies that you saw, and 1,000 seconds at 10 milliwatts per square centimeter was equal to 10 joules per square centimeter, which is the optimal light dose that you saw.

DR. DRAKE: Okay. I jotted down the hands as I saw them go up, so the next hand I saw was Dr. Mindel. I think I've got all of you down, so we'll get to everybody here.

DR. MINDEL: The inclusion criteria for Grade A was palpation as well as vision, but the success was vision only, that it looked clearer. I'm just wondering why there was no palpation for complete clearing as well as visual.

DR. MARCUS: I'll defer to Dr. Piacquadio on that.

DR. DRAKE: Dr. Piacquadio, would you mind standing up so that everybody can see and hear you?

DR. PIACQUADIO: Sure.

DR. DRAKE: Thank you.

DR. PIACQUADIO: The question was, with respect to the Grade 1 lesions, the success criteria per protocol, he's saying, basically only had a visual element to its evaluation rather than a visual or palpable element. I must confess, I don't remember that section to that level of detail in the protocol without looking. I can tell you as an investigator performing those trials and as a dermatologist, I think all of them were both tactically and visually evaluated.

~~DR. MARCUS: I can speak to the Phase III~~

protocol, and the protocol requirements for a complete clearing were both visual and tactile complete clearing, the design of the protocol.

DR. PIACQUADIO: In fact, we actually used 2x head loops to evaluate these patients, but that's just me.

DR. DRAKE: I'm going to interrupt my list here with the FDA.

Dr. Okun, I think you have a question?

DR. OKUN: Yes. Actually, I can help you, in that I happen to have that information, in that a clearing in the Phase III protocols actually was that adherent scaling plaques would no longer be evident on treated skin when palpated. So there was both visible and palpation as part of the efficacy endpoint.

DR. DRAKE: Thank you.

Dr. DiGiovanna?

DR. DiGIOVANNA: Actually, I had two questions. The Levulan is applied topically, preferably, let's say, in an afternoon. The patient is told to not wash that area and to return the next day, when it's washed off with water. I assume that means that it is able to be moved around throughout that period of 14, 16 hours. What is to keep it from being moved by the hand into the eye, rubbed on a pillow during sleeping? Because most of these will be

overnight. Has that been a problem with photosensitization, or is that something that would be envisioned?

DR. MARCUS: That's a very good question. There have been no problems with photosensitization of any adjacent areas such as you might expect from rubbing or smearing, and in the actual application, because of the hydroalcoholic nature of the solution, the drying is very rapid and virtually complete.

DR. DiGIOVANNA: The second part of my question is that the increase in efficacy at 12 weeks over 8 weeks, is that because of the second treatment at 8 weeks, or was that also seen in some of the lesions that were not treated again?

DR. MARCUS: Any lesions that did not respond at 8 weeks were retreated.

DR. DiGIOVANNA: Thank you.

DR. DRAKE: Dr. Stern was next.

DR. STERN: Yes. In terms of clarification of the subset analysis, I notice that as is in clinical practice, success rates -- at least in my experience -- on the scalp were substantially lower than they were on the face. I also noted that Type 2 lesions were substantially less successful than Type 1 lesions with respect to

clearance.

My question is, what about Type 2 lesions on the scalp? I know it's small numbers, but I have a concern because in some ways those are the most clinically relevant lesions, if you look at what some people would believe are lesions that are more likely to be troublesome in the future. How good is the efficacy there, since scalp in general didn't do terrific compared to the face?

DR. MARCUS: Indeed, the Type 2 lesions on the scalp, interesting enough -- I have a backup slide, but I wonder if, in the interest of time, I could just defer your question, because I believe -- and I don't know if it's good to ask, or traditional, but I believe Dr. Okun is going to address this in his presentation.

DR. DRAKE: Is that correct, Dr. Okun?

DR. OKUN: Yes.

DR. DRAKE: Then that would be fine.

Dr. Abel?

DR. ABEL: My question was exactly the same as that of Dr. Mindel's regarding the palpation of the lesions, because I think that's very important. Photographs don't capture these early AKs that are not all visible, but palpable.

~~And going back to the definition of defining a~~

complete response, on page 87, I wonder if that could be clarified. It says, "As a complete response, it was designated as a complete response only if the lesion had completely cleared and if adherent scaling plaques of AKs were no longer evident on the surface of treated skin when palpated." That's a little confusing.

DR. MARCUS: I'll defer to Dr. Piacquadio.

DR. PIACQUADIO: Well, again, the question is this term "complete response." Admittedly, it is confusing in the protocol, because the term is used in reference to the outcome or reaction of an individual lesion, as well as these two criterion that are applied at 75 percent and 100 percent. So complete response on an individual lesion is analogous to being completely cleared or gone. When complete response is used for the global criteria, which apply to all the lesions treated in an individual, four to 15, I think that's where the confusion comes in. It depends on what criteria you're applying, the 75 percent or the 100 percent.

DR. ABEL: I'm talking about an individual lesion. Is it palpable, or is it not? Is there scale, or is there not?

DR. PIACQUADIO: If the lesion resolved, it is ~~both clinically not evident visually as well as palpably.~~

DR. ABEL: All right. Just one comment as to the comparison between 5-FU. A statement was made that these patients heal faster than with 5-FU, but I think that's very difficult to compare, because we all know that 5-FU is applied to the general involved skin area, whereas these are spot treated.

DR. PIACQUADIO: That's a very valid assessment. There are some people, at least in Southern California, that do spot treat with 5-FU, as amazing as that seems, but I think that is a valid point.

DR. DRAKE: Dr. Lavin?

DR. LAVIN: I was interested in hearing what the distribution of the lesion severity was for the face and on the scalp, roughly if you knew what that was at baseline for the pivotals.

DR. MARCUS: That, again, is going to be covered by Dr. Okun in his discussion.

DR. DRAKE: Dr. Miller, you're next.

DR. MILLER: This is just a point of clarification.

Dr. Piacquadio, how important is it when you break these ampules for the mixture to be truly mixed? You said you only have to shake it for 2 to 3 minutes, and ~~that's a very long shake if indeed you do have to do this~~

for 2 to 3 minutes, if you're timing yourself. Did you just say that as an aside, or must you do that?

DR. PIACQUADIO: Well, I may ask Sam or Allyn to comment on that. It was set up that way in the protocol, and when you do a trial, you do it per protocol.

Would you like to comment on that, Allyn?

DR. GOLUB: During development, studies were done measuring the dissolution rate and the amount applied following 1 to 3 minutes of shaking. There were no real differences between those. We've recommended 3 minutes just to make sure that all the contents are completely mixed. We think that 3 minutes is the right number to use, but if a little less than 3 minutes happens to be used, we don't think there will be significant differences.

DR. DRAKE: Ms. Cohen?

MS. COHEN: If I understand correctly, this drug has already been approved? So anything we ask is really already a fait accompli and it doesn't make any difference?

DR. WILKIN: No.

(Laughter.)

MS. COHEN: I needed clarification. Thank you.

DR. DRAKE: I may have misspoken. If we look
~~at the questions that were laid out in front of us, the FDA~~

made a statement that in the data that's been presented to the FDA that they've evaluated, I think -- and it's quoting here -- it says it appears from the data presented that this is efficacious. So I may have misspoken.

Dr. Wilkin, if I did, I apologize. Please help clarify.

DR. WILKIN: Well, actually, we've gotten to the point where we would describe it as approvable.

DR. DRAKE: Okay.

DR. WILKIN: But approval has not occurred yet.

MS. COHEN: Well, I have some pragmatic questions, to begin with. Apparently this has to be applied by a professional. Is that correct? So the patient does not get a prescription, but has to go to a dermatologist in order to get that applied, and then they have to return again.

DR. MARCUS: For the treatment.

MS. COHEN: For the treatment.

DR. MARCUS: The patient can have the diagnosis of AKs done and the treatment, the application, at the same time.

MS. COHEN: Well, there are some practical things, in my mind, in terms of people who have to work, in terms of people who might not have enough money to do some

of these things, so it might be a little more difficult.

But I'm also looking at that nothing was done on fertility studies, there have been no animal studies. There are a lot of things that I see here that have not been done yet. So I'm a little confused as to it's approvable, so I guess if it's approvable, I better not ask these questions.

DR. MARCUS: I would be very happy to respond to your questions, but I will say to you that the agency has issued an approvable letter to the company stating no issues such as those you've mentioned as to be required for approval.

I will tell you that, in the interest of your comfort perhaps, there is a human model for overdosing of this drug for a lifetime, called porphyria, in which patients -- and Dr. Lim or Dr. Poh-Fitzpatrick on our group can speak to that. These patients live their entire life overproducing both protoporphyrin-9 or ALA. We have followed a cohort of these patients by a retrospective data collection for over 20 or 30 years of their medical history, and we have looked to them for signs of birth defects and of excessive development of any cancers, and what we have found is that the incidence of neoplasms or of birth defects does not exceed that of the general

population, and indeed we have submitted this data to the FDA as a human toxicology model.

Dr. Lim, would you care to comment?

MS. COHEN: Now, the other question I have is, a lot depends upon discipline of the patient, that they keep covered, they don't expose themselves. What about people who live in very sunny places, like Arizona or Florida, where there's a lot of sun out there? What happens?

DR. MARCUS: Dr. Piacquadio lives in sunny California. I think he could speak to that.

DR. PIACQUADIO: Yes, I think that's a very valid question. I can tell you at least patients in our trial did not have a problem with that particular issue, and even though it's a valid concern, it doesn't seem to be one in practice that is of importance.

DR. DRAKE: Okay. I want to try to move on to the FDA presentation, unless it's a very important one on clarification, because we're drifting strongly toward discussion again.

All right. I would like to ask the FDA, then, for their presentation, and I want to thank the sponsor, and don't leave. During the discussion, we may have more questions for you.

Let's now turn it over to -- Brenda Vaughan, are you starting out? I'm sorry. I'm looking at the wrong page. I'm not confused. We've only been doing this for 2 days.

Dr. Okun, would you please start? Thank you.

DR. OKUN: Yes, please.

DR. DRAKE: Brenda, I bet I gave you some excitement for a moment, didn't I?

(Laughter.)

DR. OKUN: If it's agreeable, I'd like to avoid repeating in my presentation the material that representatives of DUSA have already presented in detail. So I will skip over some of these slides very rapidly to avoid repetition.

Next slide.

As already mentioned, the indication is treatment of actinic keratoses of the face and scalp, and what's novel here is that this is the first drug/device designed to spot treat discrete actinic keratoses.

Next slide.

Dr. Marcus has already covered the proposed mechanism of action, so I think I'll skip this slide and the one subsequent to it.

~~Skip this one, too, please.~~

Sponsor evaluated the pharmacokinetics of Levulan-induced fluorescence in actinic keratoses and adjacent skin in 12 subjects. This graph depicts the change in fluorescence over time, with the solid triangles being the fluorescence of the actinic keratosis lesions, and the open triangles that of adjacent skin. What's clear from this graph is that there's little selectivity between Levulan application to actinic keratoses versus adjacent skin sites. Peak intensity of fluorescence is reached at about 12 hours, with a half-life of approximately 30 hours. Fluorescence decreases to about a third of the peak intensity by about 40 hours after application.

Next slide.

Dr. Piacquadio has already discussed a lot of the details of the Phase III protocols. There were two independent Phase III trials, ALA-018 and ALA-019, that had identical clinical protocols performed to support this NDA, and to reiterate just a few of the salient features of the enrollment criteria, four to 15 non-hyperkeratotic actinic keratoses on either the face or scalp to be enrolled. Very thick and/or hyperkeratotic actinic keratoses were excluded from being target lesions. Subjects were men and non-pregnant women over the age of 18.

Next slide.

Baseline Visit A, the Levulan or vehicle was applied to discrete lesions -- spot treatment -- by investigators. The instructions in the protocol to the patients were to avoid direct exposure of target sites to sunlight or other high-intensity light sources, including tanning light devices, to wear appropriate light-protective clothing, and not to wash target lesions.

Now our devices reviewer, Mr. Felten, is going to present just a few overheads of the device.

MR. FELTEN: I don't really think I need to. I think the company has adequately shown you the pictures of what the device looks like.

One comment I will add, though, is that the company has done a very good job in providing us the safety data we would require for such devices in terms of the stability of the output and also the light safety in terms of both the blue light and the UV, and we actually think they've done an excellent job with the device descriptions.

DR. DRAKE: That's a fantastic presentation.

(Laughter.)

DR. OKUN: Next slide, please.

Approximately 14 to 18 hours after application of the drug, 10 joules of blue light with a wavelength maximal of 417, plus or minus 5 nanometers, at 10

milliwatts per centimeter squared was administered to the face or scalp using the device you've seen. In follow-up visits, patients came back 24 hours after light exposure at and Weeks 1, 4, 8, and 12. Unblinded investigators assessed patients for occurrence and severity of adverse events.

Because it was anticipated the occurrence of adverse events would unmask allocation to treatment -- next slide -- blinded investigators did the efficacy assessments at Weeks 4, 8, and 12, and as already mentioned, patients with persistent target lesions at Week 8 were eligible for retreatment. The primary efficacy endpoints did not use patient assessment, investigator assessment, and I should mention parenthetically, since there was some discussion about comparisons between 5-fluorouracil and ALA, that in this study there were no prospective comparisons of either efficacy or tolerability. The information that was presented was patients' recollections of their experience with past treatments of their actinic keratoses.

Efficacy endpoints, the primary was at Week 8, follow-up was at Week 12, which included patients whose target lesions were retreated at Week 8.

Next slide.

~~If this issue hasn't been clarified yet,~~

hopefully we can clarify it here, that the primary efficacy variable was 100 percent complete response rate in our analysis, which was the percentage of patients with all target lesions cleared, and the definition in the protocol, adherent scaling plaques no longer evident on treated skin surface when palpated. This was considered a satisfactory endpoint, because Levulan was designed to treat discrete lesions rather than areas of skin.

Other efficacy variables considered were the 75 percent complete response rate, which is percentage of patients with 75 percent more of their actinic keratosis target lesions cleared, and the lesion response rate, which was the percentage of target lesions cleared.

Now I'm going to ask our statistics reviewer to discuss some of the efficacy results.

MS. FARR: Thank you.

My name is Shahla Farr. I'm the biostatistical reviewer for this NDA. Today I will be presenting the efficacy aspects of Levulan solution, except now I will be presenting them in each individual study separately.

The sponsor has submitted two identically designed multicenter, investigator-blinded, randomized, unbalanced parallel group, vehicle- and blue-light-controlled pivotal studies in patients with multiple